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Survival after squamous cell and basal cell carcinoma of the skin: a retrospective cohort analysis

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Abstract

A retrospective cohort analysis of survival after keratinocyte cancer (KC) was conducted using data from a large, population-based case control study of KC in New Hampshire. The original study collected detailed information during personal interviews between 1993-2002 from individuals with squamous (SCC) and basal (BCC) cell carcinoma, and controls identified through the Department of Transportation, frequency-matched on age and sex. Participants without a history of non-skin cancer at enrolment were followed as a retrospective cohort to assess survival after either SCC or BCC, or a reference date for controls. Through 2009, cancers were identified from the New Hampshire State Cancer Registry and self-report; death information was obtained from state death certificate files and the National Death Index. There were significant differences in survival between those with SCC, BCC and controls (p=0.040), with significantly greater risk of mortality after SCC compared to controls (adjusted hazard ratio [HR] 1.25; 95% confidence interval 1.01-1.54). Mortality after BCC was not significantly altered (HR 0.96; 95% CI

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0.77-1.19). The excess mortality after SCC persisted after adjustment for numerous personal risk factors including time-varying non-skin cancer occurrence, age, sex and smoking. Survival from the date of the intervening cancer, however, did not vary (HR for SCC 0.98; 95% CI 0.70-1.38). Mortality also remained elevated when individuals with subsequent melanoma were excluded (HR for SCC 1.30; 95% CI 1.05-1.61). Increased mortality after SCC cannot be explained by the occurrence of intervening cancers, but may reflect a more general predisposition to life threatening illness that merits further investigation.

Keywords

squamous cell carcinoma; basal cell carcinoma; survival

BACKGROUND

Each year in the United States, between one and 3.5 million keratinocyte cancers (KC) are diagnosed, consisting primarily of basal cell (BCC) and squamous cell carcinoma (SCC).[1,2] In some populations, the incidence of KC has tripled over the past 30 years [3] resulting in substantial morbidity and treatment expense. KC, and particularly BCC, rarely metastasize and although their treatment may present substantial challenges, they are generally curable. There is an increased incidence of other cancers among individuals with KC,[4-25] but it is unclear whether this is due to an individual's susceptibility to cancer, environmental exposures, or a combination of factors. There are also indications of reduced relative survival after KC, particularly after SCC, but the studies that have examined this in detail provide mixed results.[2,6-33] Population-based data suggest that the 5-year relative survival rates (RSR) after BCC are close to 100%, and some estimates even suggest that BCC is associated with better survival than population controls.[27] In contrast, 5 year RSR after SCC is closer to 90%, but the reason for these effects is unclear.[5,32]

We previously studied risk factors for KC in a large, population-based case control study of individuals with incident BCC or SCC and controls, using a combination of detailed personal risk factor data. Subsequent cancers were examined in a retrospective cohort analysis of the same individuals, having ascertained cancers and deaths via linkage to the state cancer registry and national and state death certificate records. In that study, the risk of subsequent cancer was significantly raised after BCC (HR 1.40; 95% CI 1.15 to 1.71) and modestly raised after SCC (HR 1.18; 95% CI 0.95 to 1.46).[25] Here, we present mortality data from the same cohort.

MATERIAL AND METHODS

Ethics Statement

This work was approved by the Committee for the Protection of Human Subjects of Dartmouth College (#21177). Participants in the New Hampshire Skin Cancer Study (NHSCS) underwent an informed consent process at enrolment. Use of data from the New Hampshire State Cancer Registry was approved by the New Hampshire Department of Public Health Services. The analytic dataset was de-identified to protect confidentiality.

New Hampshire Skin Cancer Study

The New Hampshire Skin Cancer Study is described in detail elsewhere.[34] Population-based surveillance was conducted for keratinocyte cancers (KC) newly diagnosed between 1993 and 2002 among New Hampshire residents, and participants were recruited for a case control study. The reference date for the study was defined as the date of diagnosis, or a matched comparable date generated for controls. Data collection occurred in three phases, with refinement of the variables collected in each phase. Personal interviews were conducted with 2,713 individuals with KC (SCC 1,170; BCC 1,543), and 1,416 controls frequency matched on age and sex; information was collected on a variety of health, behavior and environmental exposures. This follow-up analysis is based on a sample size that was determined according to the goals of the original case control study.

New Hampshire State Cancer Registry

The New Hampshire State Cancer Registry (NHSCR) is a population-based registry of reportable incident cancers covering the ~1.2 million residents of New Hampshire. Data from 1995 onwards meet the North American Association of Central Cancer Registries standards for quality and completeness.[35] Data from 1986-1995 are partially complete, and some information is available on cases diagnosed before 1986 and in other states. Deaths are identified through annual linkage with state death certificates and the National Death Index.

Exclusions of individuals with a prior history of cancer

Participants were excluded from the mortality analyses if, before the reference date, they had a diagnosis of cancer other than KC or melanoma that had been identified either through NHSCR or self-report at study enrolment. Self-reports of major cancers have previously been shown to be fairly reliable [3637] and were likely to provide an accurate diagnosis in cases that may not have been identified through NHSCR i.e., if they occurred outside New Hampshire or before 1995. To maximize consistency between self-reported and registry cancers, we considered *in situ* malignancies (excluding cervix and prostate) in NHSCR as "prior" cancers.

Ascertainment of cancer and death following KC

We linked the NHSCS database with NHSCR to identify incident cancers through 2009, using definitions of reportable cancers from 2008.[38] Invasive cancers were defined as those of stage 1 or higher, or bladder cancers of any stage (including in situ, stage 0). In addition, we obtained self-reported cancer data via a mailed survey to all participants who were not known to have died. This survey collected information on cancer diagnosis and cancer site, date, treating hospital or other facility, and the type of treatment given; self-reported cancers that had not been confirmed by NHSCR were adjudicated by one investigator (JR) and determined to be "confirmed" or "unconfirmed". We linked the NHSCS database with NHSCR and with the New Hampshire death certificate database for the period 1993-2009 and with the National Death Index (NDI) through December 31, 2009 to identify deaths nationwide. Analyses of disease-specific mortality were based on the underlying cause of death determined from death certificates. The underlying cause is identified from conditions reported in the medical certification section of the death certificate using an algorithm of

selection rules standardized by the World Health Organization and implemented in the Automated Classification of Medical Entities system.[3940]

Statistical analysis

The endpoint for our primary analyses was the time from the reference date to either death or to December 31st, 2009. We used Cox proportional hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CI) associated with mortality for BCC and SCC cases (separately) versus controls. For all analyses, except where stated, the HRs were adjusted for age, sex, and smoking (in pack-years: 0, 0.l-20, 20.1-40, >40). To investigate the effects of subsequent diagnosis of cancer on survival we first stratified by subsequent cancer status and performed interaction tests to evaluate the effects of subsequent cancer on group differences (BCC, SCC and control). We then determined the overall differences between BCC, SCC and control groups by fitting subsequent cancer as a time-varying factor. Proportional hazards assumptions were tested by observation of the survival curves and using a global test based on the Schoenfeld residuals.

In secondary analyses, we similarly assessed mortality in the subgroups of participants with and without a subsequent melanoma. In a subgroup analysis of those with a subsequent cancer, we assessed survival dated from the diagnosis of that cancer. Finally, we performed sensitivity analyses to assess the effect of including cancer cases only identified through death certificates ("death certificate only", or DCO).

All analyses were conducted using Stata v11.

RESULTS

Of the 4,223 individuals enrolled in the case control study, 639 were excluded because of a prior non skin cancer at the time of enrolment leaving 3,584 individuals for analysis (Table 1). Adjusted models included between 3,407 and 3,584 individuals due to missing covariate data.

During an average of >10 years of observation, 587 eligible participants had subsequent reportable cancer and 561 participants died with or without subsequent cancer (Table 1). Overall, there were significant differences in mortality between the three case groups (controls, BCC, SCC) after adjustment for age, sex, smoking and subsequent cancer (time-varying), with poorer survival after SCC relative to controls than after BCC relative to controls (Table 2, Figure 1). Specifically, a statistically significantly higher mortality was seen among individuals with SCC compared to controls (HR 1.25; 95% CI 1.01 to 1.54). Mortality among those with BCC was not statistically significantly different than controls. In sensitivity analyses, exclusion of in situ cancers did not materially alter the findings (data not shown).

In the same model, subsequent cancer was independently associated with survival, after adjusting for age, sex, and case group (HR 2.58; 95% CI 2.16 to 3.09) and this association did not appear to differ between case groups (p for interaction = 0.95) (Table 2 and Figure 1). When time-varying subsequent cancer status was excluded from the model, the relative

differences in mortality seen by case group were essentially unchanged (data not shown), and the mortality associated with SCC remained high (HR 1.24; 95% CI 1.01 to 1.53). Survival measured from the date of subsequent cancer diagnosis, instead of the date of KC diagnosis, did not differ significantly between groups. In particular, survival after SCC in this subgroup analysis was similar to that in controls (HR 0.98; 95% CI 0.70 to 1.38).

Analyses of survival after a subsequent melanoma were conducted without adjustment for age, sex or smoking due to the small numbers of participants (N=89). Among those who developed a melanoma after the reference date, those with KC did so substantially earlier than controls (BCC 265 days; 95% CI 233 to 298, and SCC 1044 days; 95% CI 1010 to 1079). Compared to controls, there was poorer survival among individuals with a subsequent melanoma in the SCC group (crude HR 1.29; 95% CI 0.26 to 6.44) and in the BCC group (crude HR 1.16; 95% CI 0.25 to 5.38), but overall, the difference between the three case groups did not achieve statistical significance (p=0.36). Among those without a subsequent melanoma (N=3,316), the patterns of survival in the case groups were similar to those seen in all participants (p=0.026), with an increased mortality risk after SCC (HR 1.30; 95% CI 1.05 to 1.61) but not after BCC (HR 0.99; 95% CI 0.80 to 1.24).

Several factors were independently related to survival (Supplementary Table 1). Higher mortality was associated with increasing age, male sex and current smoking, with a three-to four-fold increased risk in those with a 40+ pack year smoking history. No clear pattern was observed with level of education or body mass index.

The most common subsequent cancers identified in the cohort were of prostate, melanoma, breast, lung and colon (Supplementary Table 2). After KC, 15% of individuals (n=59) experienced two or more subsequent cancers during the observation period compared with only 7% (n=14) controls.

The survival probabilities, after adjustment for age, sex and smoking, reflected the relative trend in survival across groups (control>BCC>SCC) for those with and without subsequent cancer and the clearly poorer survival among those with subsequent cancer (Figure 1). Death certificates most commonly attributed death to cancer among those who had a confirmed subsequent cancer (with lung cancer being the most common of these), and cardiovascular/ respiratory causes among those who did not (Supplementary Table 3).

When we conducted sensitivity analyses (not shown) to assess the impact on our results of inclusion of “death certificate only” cancers (i.e. those not confirmed by medical records, N=17), our results were essentially unchanged.

DISCUSSION

Our results indicate differences in survival among individuals with SCC, BCC and controls during an average of more than 10 years of follow-up. Those with SCC had 25% higher mortality risk than controls after adjusting for age, sex, pack-years of smoking and time-varying subsequent cancer occurrence. The adjusted hazard ratio for mortality after BCC vs controls was close to 1 despite a 40% higher risk of intervening cancer,[25] indicating that there may be important differences between the major histologic types of KC with respect to

survival.[25] A series of Danish studies also identified survival differences between SCC and BCC, with mortality 29 to 61% higher after SCC and 3 to 11% lower after BCC.[26-29] Finnish data from the 1960s and 1970s indicated relative survival rates close to 100% for BCC at 5 and 10 years; and for SCC, 90% at 5 years and 83-87% at 10 years.[32] These, and our own data indicate that future studies of cancer and mortality after KC should report BCC and SCC separately as analyses that pool these two distinct histologies are likely to be uninterpretable.

Our findings suggest that the increased mortality after SCC cannot be explained by subsequent cancer. Although SCC was independently associated with increased mortality, adjustment for time-varying subsequent cancer status in the multivariable model did not materially reduce the excess mortality after SCC. Moreover, the excess mortality after SCC cannot be explained by mortality from cutaneous SCC itself as this is infrequently fatal.[41] Mortality after SCC also remained substantially elevated even after excluding individuals with subsequent melanoma. It is possible that individuals with SCC are at greater risk of developing other diseases that reduce life expectancy; all of our models adjusted for smoking and we assessed other risk factors, but other lifestyle factors may have contributed. For example, the Danish studies identified an excess of deaths due to diseases linked to smoking, alcohol and immune suppression.[26-28] We did not have the statistical power to assess these questions in our study. We cannot yet provide new targets to clinicians for prevention strategies, but our results highlight the need to identify more specifically the genetic and behavioral risk factors for mortality in SCC patients that may offer new opportunities for prevention.

Another possible explanation for increased mortality after SCC is a tendency to experience subsequent cancers with a worse prognosis; several studies have reported substantially higher mortality after cancer when individuals have a prior SCC [3042-44] or BCC [21 43]. Our findings do not support those observations; among those who developed a subsequent cancer, we found no evidence of a difference between case groups in survival measured from the subsequent cancer diagnosis. In contrast, Hjalgrim reported that non Hodgkin's lymphoma was associated with 51% higher mortality after BCC and 75% higher after SCC, and that a more recent SCC was associated with worse prognosis [43]. Brauer found that metastases from melanoma were more likely in individuals with a prior KC (odds ratio 2.89; 95% CI 1.33 to 6.26), and among those with a metastasis, a history of KC increased the risk of early (versus late) metastasis (OR 4.83; 95% CI 1.04 to 22.39)[45]. In colorectal cancer, lymph node involvement at the time of diagnosis was more likely in individuals with a history of KC than in those without.[46] Nugent could not explain the increased mortality after KC in breast and colorectal cancer in terms of differences in stage[21], and others have not provided evidence that cancers were diagnosed at a more advanced stage after SCC.[214748] Although we did not observe any differences in mortality following cancer among KC patients, we had a limited ability to assess specific cancers, and stage at diagnosis and site- and stage-specific mortality for subsequent cancers. Further, a shorter interval between diagnoses of KC and subsequent cancer might be expected if increased medical surveillance associated with a KC diagnosis leads to earlier identification of a subsequent cancer; but if that were true, we would expect a better prognosis. It is possible that potentially toxic modalities such as radiotherapy might lead to subsequent morbidity and mortality; however,

SCC is infrequently treated with radiation. In an academic hospital-based cohort study, initial treatment of SCC involved radiotherapy in fewer than 4% of cases. [41] It is likely that the proportion receiving radiotherapy in our cohort would have been even lower than 4%, because a hospital-based cohort would include a higher proportion of more complex cases referred for specialist treatment.

Limitations of this study include the possibility of misclassification of cancer diagnoses and deaths as a result of inaccuracies in the cancer registry and death databases, or due to the linkage algorithms. In addition to lack of statistical power, lack of confidence in the ability of death certificates to provide accurate cause of death data[4950] prevented an effective assessment of cause of death in our cohort. We did not identify new diagnoses of keratinocyte cancers during follow-up; undocumented changes in case group (e.g controls becoming cases) might lead to a conservative bias in our results. Power limited our ability to assess mortality following specific cancers, and to assess stage at diagnosis and site- and stage-specific mortality for subsequent cancers. Lastly, our findings are based on a cohort from northern New England, which experiences extreme seasonal weather; our ability to generalize these findings to other populations thus cannot be certain.

In conclusion, in our cohort of individuals with SCC, BCC and age and sex-matched controls with detailed exposure and medical history data, we identified increased mortality after SCC, but not BCC, which does not appear to be attributable to the increased frequency of other cancers after keratinocyte cancer. It will be important to identify more specific risk factors for mortality after SCC for future preventive strategies to address this issue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Keratinocyte cancers are rarely fatal but are associated with increased risk of subsequent cancer and mortality for reasons that are unclear. During >10 years' follow-up, we identified a 25% increased mortality after SCC compared with controls, but mortality in those with BCC was unaffected. Despite examining a wide range of personal risk factor data, we could not explain the excess mortality in terms of intervening non-skin cancers, melanoma, smoking, or other personal characteristics.

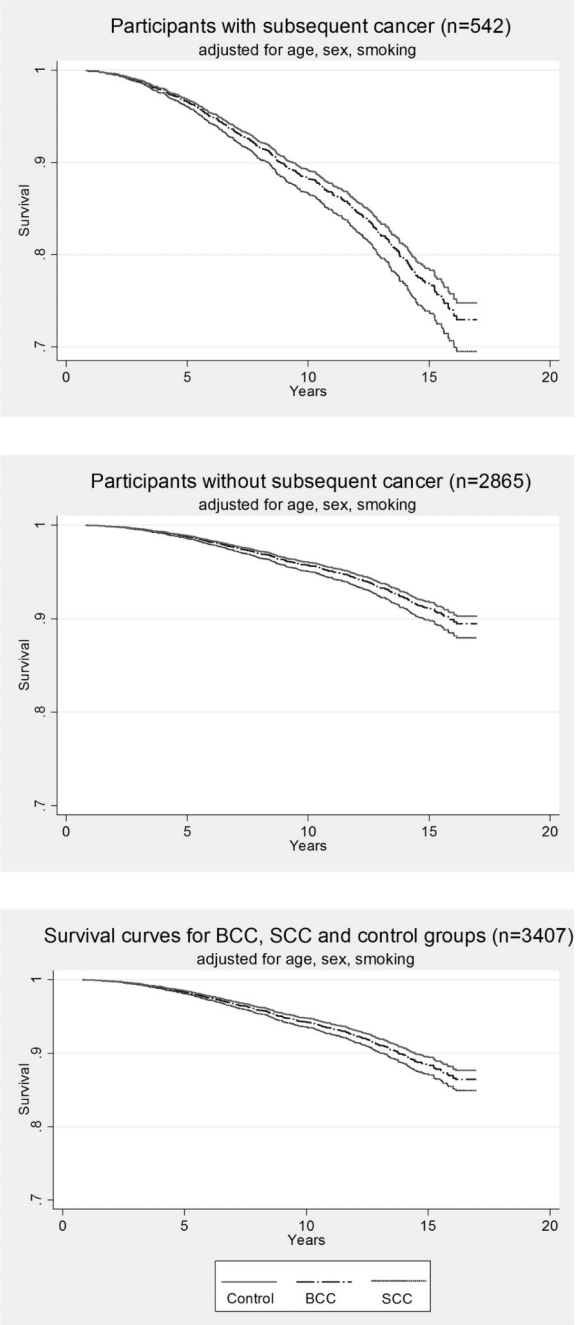

Figure 1.

Survival curves after keratinocyte cancer for participants with subsequent cancer, without subsequent cancer, and all

Total with subsequent cancer (N=542) does not equal 587 due to missing covariate data

Table 1

Inclusion and exclusion of study participants and follow-up after enrolment

	Controls			Basal cell cancer (BCC)			Squamous cell cancer (SCC)		
	Men	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
Participants in case control study	833	665	1,498	813	787	1600	700	425	1,125
Mean years of follow-up	10.1	9.2		10.3	9.4		9.8	9.5	
Cancer status at reference date:									
Participants ineligible for analysis[1]:									
Prior internal cancer	73	84	157	130	107	237	160	85	245
Participants eligible for analysis:									
No prior cancer	741	578	1,319	616	656	1,272	508	330	838
Prior melanoma only	19	3	22	67	24	91	32	10	42
Total	760	581	1,341	683	680	1,363	540	340	880
Participants diagnosed with cancer after reference date:									
(Ineligible participants)	(16)	(15)	(31)	(36)	(26)	(62)	(50)	(26)	(76)
Eligible participants	131	66	197	145	74	219	119	52	171
Tumors after reference date among eligible participants[2]:									
In situ	7	4	11	15	18	33	13	9	22
Invasive	106	59	165	134	54	188	97	40	137
Unstaged	7	2	9	13	6	19	10	3	13
Unknown	24	3	27	16	6	22	20	5	25
Total	144	68	212	178	84	262	140	57	197
Deaths in eligible participants:	156	47	203	121	48	169	142	47	189
Confirmed subsequent cancer	64	21	85	61	21	82	61	17	78
No confirmed subsequent cancer	92	26	118	60	27	87	81	30	111

Follow-up time is the time from initial enrolment interview to death or December 31, 2009

[1] Participants with cancer of any organ except the skin, diagnosed before the reference date, were excluded from the main analyses.

[2] A participant with multiple cancers is counted multiple times. In situ is defined as stage 0 except bladder (excludes in situ prostate and cervix). Invasive is defined as stages 1-4, or stage 0 bladder.

Table 2

Hazard ratios for mortality after keratinocyte cancer among participants without a prior history of cancer[1] (N=3407)

	HR (95% CI)	Significance tests
Case group		
Control	1.00	P for overall difference between 3 case groups 0.040
BCC	0.96 (0.77 to 1.19)	
SCC	1.25 (1.01 to 1.54)	
		P for comparison of HR for BCC vs. SCC = 0.019
Subsequent cancer[1]	1.00	
No	2.58 (2.16 to 3.09)	
Yes		P < 0.001
Case group × subsequent cancer interaction assessed in fully adjusted model[1]		P for interaction [case group × subsequent cancer] = 0.95

[1]Model includes the following factors: case group (control, BCC, SCC), subsequent cancer (time-varying binary), and covariates: age, sex, pack-years smoking. Estimates presented are mutually adjusted.